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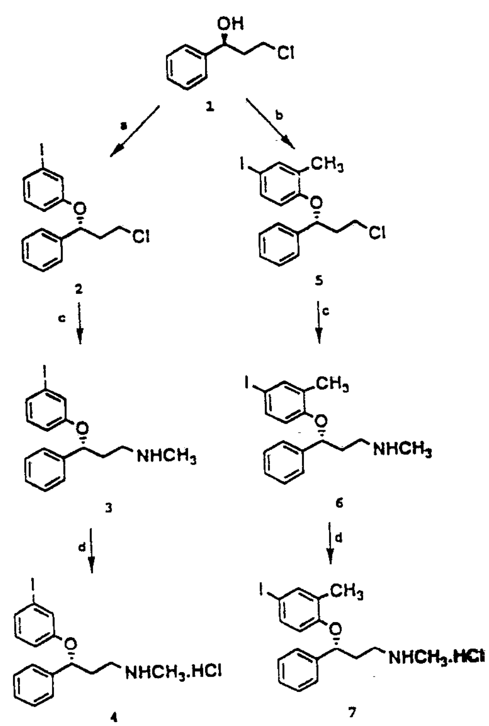
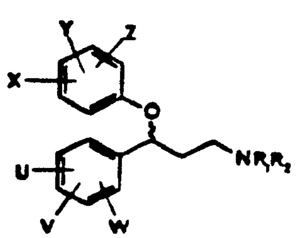
(54) Title: SEROTININ REUPTAKE INHIBITORS FOR S.P.E.C.T IMAGING

(57) Abstract

Disclosed are novel compounds for CNS neurotransmitter systems, especially for the neurotransmitter serotonin, which have formula (I), where each of U, V, W, X, Y and Z is independently selected from the group consisting of hydrogen; halogen; C_1-C_4 alkyl; C_1-C_4 alkyl substituted with one ore more moieties selected from halogen atoms and hydroxy groups; C_1-C_4 alkoxy; C_1-C_4 alkoxy substituted with one ore more moieties selected from halogen atoms and hydroxy groups; C_1-C_6 heterocycles; C_1-C_4 thioalkyl; NR_3R_4; $-R_5$-A-R_6; and -A-R_7; CN; SO_2R_8; $-NHCONH_2$; and $C(O)NR_3R_4$; each of R_1, R_2, R_3 and R_4 is independently selected from the group consisting of hydrogen and C_1-C_4 alkyl; each of R_5 and R_6 is independently a C_1-C_6 alkyl; R_7 is selected from the group consisting of H, C_1-C_6 alkyl, C_1-C_6 heterocycles or -A-R_5; R_8 is selected from the group consisting of C_1-C_4 alkyl and NR_3R_4; A is selected from the group consisting of S, N and O; provided that at least one of U, V, W, X, Y and Z is a halogen atom; and pharmaceutically acceptable salts thereof.





(I)

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AT	Austria	FI	Finland	ML	Mali
AU	Australia	FR	France	MN	Mongolia
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SEROTONIN REUPTAKE INHIBITORS FOR S.P.E.C.T IMAGING

Field of the Invention

This invention relates to novel compounds for CNS neurotransmitter systems, especially for the neurotransmitter serotonin, which can be utilized to image neurotransmitter reuptake systems in the brain.

Background of the Invention

Depression, with its related conditions, is one of the most common mental disorders in the United States. It is estimated that about five percent of the adult population experiences a depressive episode in their lifetime that requires antidepressive drug therapy.

A chemical in the human brain, called serotonin, has been linked with depression and with other psychiatric disorders such as eating disorders, alcoholism, pain, anxiety and obsessive-compulsive behavior. Serotonin is a neural transmitter, a chemical that is used to send messages from one brain cell to another. Neurotransmitters bind to special receptor proteins in the membrane of nerve cells, like a key in a lock, triggering a chemical reaction within the cell. It has been found that drugs that enhance transmission of serotonin in the brain are useful in treating major psychiatric disorders such as depression. These drugs act as serotonin-uptake inhibitors.

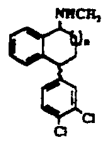
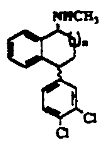
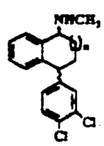
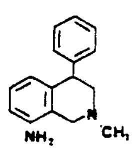
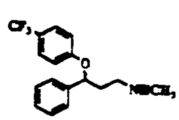
Upon appropriate stimulation, the serotonin neuron in the brain releases serotonin. Once released, the serotonin is free for a short period of time before it is either metabolized or picked up again by another receptor protein on a serotonin neuron (called "serotonin reuptake"). Either

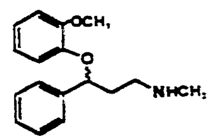
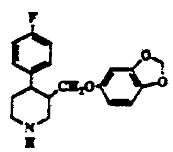
metabolism or reuptake reduces the amount of free serotonin available. If reuptake is reduced, there is more serotonin available for transmission. Certain anti-depressive drugs, such as Prozac, operate to inhibit serotonin reuptake by binding with the serotonin receptor protein, effectively blocking the binding of the protein with the serotonin. Although Prozac has been found to be an effective anti-depressant treatment, it has side effects which can be serious. Prozac is known to bind to the serotonin receptor protein, but the responses of patients can differ widely. Some patients experience greater binding than others. If a patient is not responding to Prozac treatment, there is currently no way to determine why that is the case. Frequently, the physician will simply administer greater doses of the drug, a practice which will not necessarily lead to better results and which can enhance undesirable side effects.

Other serotonin reuptake inhibitors are also known which tend to be better tolerated than tricyclic agents such as Prozac. The structures of several of these inhibitors, and their affinity constants for the serotonin reuptake system (5-HT) as well as for other neurotransmitter reuptake systems, norepinephrine (NE) and dopamine (DA), are presented below in Table 1.

Table 1

Inhibition of Monoamine Uptake by Antidepressants in Rat Synaptosomes (Ki in nM)

Compound		DA	NE	5-HT
 cis, 1S,4S, n=1 Sertraline		520	720	70
 trans, 1R,4S, n=1 Tametraline		60	20	50
 n=0	trans	2000	90	0.58
	cis	860	34	0.03
Indatraline				
 Nomifensine		48	5	5000
 Fluoxetine		1590	289	25

Compound	DA	NE	5-HT
 Nisoxetine	365	670	3.8
 Paroxetine	---	350	1.1

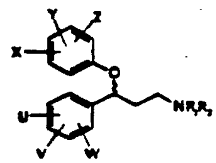
Although therapy with several of these drugs may not be accompanied by side effects as serious as those sometimes attributed to Prozac, there is still a need for a method to monitor the treatment of patients with the drugs as well as a method for studying the efficacy of such drugs.

New and powerful imaging methods which enable one to assess the living brain *in vivo* and thereby monitor the effectiveness of drugs and substances that affect brain chemistry have recently been developed. Methods such as positron emission tomography (PET) and single photon emission tomography (SPECT) involve the administration to a patient of radioactive tracer substances comprising a ligand that binds to presynaptic or postsynaptic neuroreceptors in the patient's brain. Emissions (primarily gamma rays which are emitted from the positrons or photons emitted from the radioactive tracer) are measured. These emissions are indicative of the number and degree of occupancy of blocking of the neuroreceptors. The number of neuroreceptors and the degree of occupancy or blocking is calculated utilizing a mathematical model, and compared with an intra-person or inter-person control, to determine the degree of drug response. Further treatment of the patient with drugs is based upon the comparisons made. By using these imaging methods to monitor the serotonin

reuptake sites, improved treatment of patients with psychiatric disorders such as depression should be possible.

Summary of the Invention

This invention relates to novel compounds of Formula I:



I

where each of U, V, W, X, Y and Z is independently selected from the group consisting of hydrogen; halogen; $C_1 - C_4$ alkyl; $C_1 - C_4$ alkyl substituted with one or more moieties selected from halogen atoms and hydroxy groups; $C_1 - C_4$ alkoxy; $C_1 - C_4$ alkoxy substituted with one or more moieties selected from halogen atoms and hydroxy groups; $C_1 - C_6$ heterocycles; $C_1 - C_4$ thioalkyl; NR_3R_4; $-R_5 - A - R_6$; and $-A-R_7$; CN; SO_2R_8; $-NHCONH_2$; and $C(O)NR_3R_4$;

each of R_1, R_2, R_3 and R_4 is independently selected from the group consisting of hydrogen and $C_1 - C_4$ alkyl;

each of R_5 and R_6 is independently a $C_1 - C_6$ alkyl;

R_7 is selected from the group consisting of H, $C_1 - C_6$ alkyl, $C_1 - C_6$ heterocycles or $-A-R_5$;

R_8 is selected from the group consisting of $C_1 - C_4$ alkyl and NR_3R_4;

A is selected from the group consisting of S, N and O;

provided that at least one of U, V, W, X, Y and Z is a halogen atom;

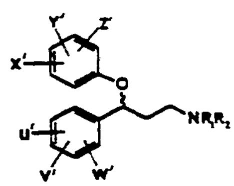
and pharmaceutically acceptable salts thereof.

As used herein, the term "alkyl" is intended to encompass straight-chained, branched and cyclic alkyl groups. Similarly, the terms "alkoxy" and "thioalkyl" encompass straight-chained and branched group. The term "heterocycle" is used to encompass ring structures in which one or more of the atoms in the ring is an element other than carbon, for

example, sulfure, nitrogen or oxygen.

Tests suggest that the compounds of Formula I bind to neurotransmitter reuptake sites, and that many of the compounds are specific to serotonin reuptake sites. When the halogen atom on the molecule is a radioactive ion, such as ^{123}I, the serotonin reuptake sites may be imaged by means such as PET and SPECT. Such imaging of the human brain may provide or suggest direct information on the location and quantitation of the reuptake sites. Direct assessment on the status of serotonin reuptake may provide evidence of how the selective serotonin reuptake inhibitors regulate the reuptake sites and may also be a diagnostic tool for individualizing the dosage for this class of antidepressants. The compounds of Formula I where the halogen atom is not a radioactive isotope will also bind to serotonin reuptake sites, suggesting therapeutic utility or use in *in vitro* binding studies. Certain of the compounds are also useful as intermediates for preparing the radioactive ion-labelled compounds.

Also included within the scope of this invention are certain novel intermediates of Formula II:



II

where one of U', V', W', X', Y' and Z' is selected from the group consisting of $Sn(R)_3$, $Si(R)_3$ and HgR, where R is C_1 - C_5 alkyl; and the others are selected from the group consisting of hydrogen; halogen; C_1 - C_4 alkyl; C_1 - C_4 alkyl substituted with one or more moieties selected from halogen atoms and hydroxy groups; C_1 - C_4 alkoxy; C_1 - C_4 alkoxy substituted with one or more moieties selected from halogen atoms and hydroxy groups; C_1 - C_6 heterocycles; C_1 - C_4 thioalkyl; NR_3R_4; $-R_5$ -A - R_6; and $-A-R_7$; CN; SO_2R_8; $-NHCONH_2$; and $C(O)NR_3R_4$; and where R_1 - R_8 and A are as defined above.

Brief Description of the Drawings

Figure 1 is a schematic illustrating a method for preparing certain (R) isomers of compounds of this invention.

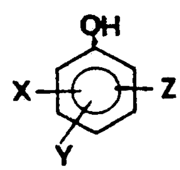
Figure 2 is a schematic illustrating a method for preparing certain (S) isomers of compounds of this invention.

Figure 3 is a schematic illustrating a method for preparing the compound iodo-fluoxetine.

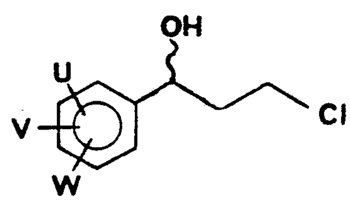
Detailed Description of the Invention

The novel compounds of Formulas I and II can exist in pure isomeric form or in racemic mixtures; this invention is contemplated to encompass the compounds in either form.

The compounds can be prepared by methods analogous to those illustrated in Figures 1 and 2 and described in the examples. Generally, a suitably substituted phenol



is condensed with 3-chloro-1-phenylpropanol or a substituted version thereof



to yield a substituted 1-chloro-3-phenyl-3-phenoxypropane. Upon reaction of this product with the appropriate amine, HNR_1R_2, the desired compound of Formula I is obtained. Pharmaceutically acceptable salts, such as bromide or chloride salts, can be prepared by methods known in the art.

Compounds of Formula I labeled with an iodide isotope can be prepared from the corresponding bromo-compound via the intermediacy of a stable, versatile tin intermediate. The bromine moiety is converted by a refluxing with dry triethylamine using tetrakistriphenylphosphine palladium catalyst. The resulting tributyltin compound can be converted to the desired iodo derivative by simply stirring with iodine

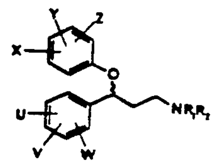
in dry chloroform at room temperature. Alternatively, the tributyltin compound can be converted by reaction with the appropriate sodium iodide salt in aqueous hydrogen peroxide. The tributyltin compounds are not the only intermediates which can be used in preparing the radiolabeled compounds. Other intermediates within the scope of Formula II may be used in an analogous manner.

Although ^{125}I isotopes are useful for laboratory testing, they will generally not be useful for actual diagnostic purposes because of the relatively long half-life (60 days) and low gamma-emission (30-65 KeV) of ^{125}I. The isotope ^{123}I has a half life of thirteen hours and gamma energy of 159 KeV, and it is therefore expected that labeling of ligands to be used for diagnostic purposes would be with this isotope. Other isotopes which may be used include ^{131}I (half life of 2 hours).

Preferred compounds of this invention are those of Formula I wherein, simultaneously or independently: (1) one of X, Y and Z is alkyl; (2) one of X, Y and Z is halogen; (3) one of X, Y and Z is ^{123}I; (4)R_1 is H and R_2 is CH_3. More preferred compounds of this invention are those of Formula I wherein, simultaneously or independently: (1) X is a 2-alkyl substituent; (2) Y is a 4-halogen substituent; (3) Z is hydrogen; (4) R_1 is H and R_2 is CH_3. The most preferred compounds are N-methyl-3-phenyl-3-(4-iodo-2-methylphenoxy)propylamine, and its pharmaceutically acceptable salts, preferably the (R)-(-)-isomer.

Specific examples of compounds contemplated within the scope of this invention are presented in Table 2.

Table 2



where R_1 and R_2 are independently selected from hydrogen, methyl, ethyle, n-propyl, n-butyl, cyclopropyl, i-propyl, i-butyl, t-butyl.

X or U	Y or V	Z or W
2-I	H	H
3-I	H	H
4-I	H	H
2-I	3-OH	H
3-I	2-OH	H
4-I	2-OH	H
4-I	3-OH	2-Me
2-I	3-OH	4-Me
3-I	2-OH	4-Me
4-I	2-OH	3-Me
4-I	3-CN	H
2-I	3-CN	H
3-I	2-CN	H
4-I	2-CN	H
4-I	3-CN	2-Me
2-I	3-CN	4-Me
3-I	2-CN	4-Me
4-I	2-CN	3-Me
2-I	3-Me	H
3-I	4-Me	H
4-I	2-Me	H
2-I	3-CF_3	H
3-I	4-CF_3	H
4-I	2-CF_3	H
2-I	3-OMe	H
3-I	4-OMe	H
4-I	2-OMe	H
2-I	3-NH_2	H
3-I	4-NH_2	H
4-I	2-NH_2	H
2-I	3-$NHCH_3$	H
3-I	4-$NHCH_3$	H
4-I	2-$NHCH_3$	H
2-I	3-$N(Me)_2$	H
3-I	4-$N(Me)_2$	H
4-I	2-$N(Me)_2$	H

Table 2 - continued

X or U	Y or V	Z or W
2-I	3-NH_2	H
3-I	4-NH_2	H
4-I	2-NH_2	H
2-I	4-NH_2	H
3-I	2-NH_2	H
4-I	3-NH_2	H
2-I	3-SMe	H
3-I	4-SMe	H
4-I	2-SMe	H
2-I	3-OMe	4-OMe
3-I	2-OMe	4-OMe
4-I	2-OMe	3-OMe
2-I	3-OMe	4-OMe
3-I	2-OMe	4-OMe
4-I	2-OMe	3-OMe
2-I	3-CH_2CH_2F	H
3-I	4-CH_2CH_2F	H
4-I	2-CH_2CH_2F	H
2-I	3-OCH_2CH_2F	H
3-I	4-OCH_2CH_2F	H
4-I	2-OCH_2CH_2F	H
2-I	3-CH_3	4-CH_3
3-I	4-CH_3	3-CH_3
4-I	2-CH_3	4-CH_3
2-I	3-OCH_2CH_3	CH_3
3-I	4-OCH_2CH_3	CH_3
4-I	2-OCH_2CH_3	CH_3
2-I	3-CH_3	OH
3-I	4-CH_3	OH
4-I	2-CH_3	OH
2-I	3-CF_3	OH
3-I	4-CF_3	OH
4-I	2-CF_3	OH
2-I	3-CH_3	4-OCH_3
3-I	4-CH_3	2-OCH_3
4-I	2-CH_3	3-OCH_3
2-I	3-CF_3	4-OCH_3
3-I	4-CF_3	3-OCH_3
4-I	2-CF_3	2-OCH_3
2-I	3-OCH_3	4-OCH_3
3-I	4-OCH_3	2-OCH_3
4-I	2-OCH_3	3-OCH_3
2-I	3-Cl	4-CH_3
3-I	4-Cl	2-CH_3
4-I	2-Cl	3-CH_3
2-I	3-CH_3	4-Cl
3-I	4-CH_3	2-Cl

Table 2 - continued

X or U	Y or V	Z or W
4-I	2-CH_3	3-Cl
2-I	3-F	4-CH_3
3-I	4-F	2-CH_3
4-I	2-F	3-CH_3
2-I	3-CH_3	4-F
3-I	4-CH_3	2-F
4-I	2-CH_3	3-F

(In this Table, the numerical prefix is intended to indicate placement of substitution on either ring of the compound.)

The compounds of this invention lend themselves easily to formation from materials which could be provided to users in kits. Kits for forming the imaging agents can contain, for example, a vial containing a physiologically suitable solution of an intermediate of Formula II in a concentration and at a pH suitable for optimal complexing conditions. The user would add to the vial an appropriate quantity of the radioisotope, e.g., $Na^{123}I$, an an oxidant, such as hydrogen peroxide. The resulting labelled ligand may then be administered intravenously to a patient, and receptors in the brain imaged by means of measuring the gamma ray or photo emissions therefrom.

The following examples are illustrative, but not limiting, of the present invention.

Melting points were determined with a Meltemp (Laboratory Devices) and are reported uncorrected. Infrared spectra were obtained with a Mattson Polaris FT-IR spectrometer. NMR spectra were determined with a Varian EM 360A spectrometer. Elemental analyses were performed by Atlantic Microlabs, Inc., of Atlanta, Georgia. All of the chemicals were of reagent grade and used without further purification.

Example 1

Preparation of [R]-(-)-N-Methyl-3-phenyl-3-(3-iodophenoxy)propylamine (Compound 4, Figure 1)

Triphenylphosphine (1.54 g, 5.88 mmole) and ethyl azodicarboxylate (8.93 mL, 1.03 g, 5.88 mmol) were added to a solution of [S]-3-chloro-1-phenylpropanol (1.0 g, 5.88 mmol) and 3-iodophenol at room temperature for 15 hours. THF was removed under aspirator vacuum. The residue was triturated with petroleum ether (3 x 15 mL). The combined fractions were concentrated, and the crude product was purified by flash column chromatography on silica gel. Elution with petroleum ether and removal of solvent afforded 1.64 g (75%) of [R]-(+)-11-chloro-3-phenyl-3-(3-iodophenoxy)propane, Compound 2, as a thick colorless liquid: $[\alpha]^{25}{}_{D}+ 1.85$ (c 5.4, $CHCL_3$); ^{1}H NMR ($CDCL_3$ 250 MHz) δ 7.40 -

7.20 (m, 7H), 6.90 - 6.76 (m, 2H), 5.34 (dd, J = 4.6, 9.2 Hz, 1H), 3.82 - 3.72 (m, 1H), 3.62 - 3.53 (m, 1H), 2.51- - 2.38 (m, 1H), 2.26 - 2.14 (m, 1H). Anal. C_{15} H_{14} Cl I O; C,H.

In a sealed tube, a mixture of Compound 2 (0.56 g, 1.50 mmol), aqueous methylamine (40%, 4 mL) and ethanol (1.5 mL) was heated at 130° C for 3 hours. The cooled mixture was poured into water (5 mL) and was extracted with CH_2Cl_2 (3 x 5 mL). The organic solution was dried, filtered and concentrated to give a yellowish oil. Flash-column chromatography of the crude produce on silica gel (5% $MeOH/CH_2Cl_2$) afforded 0.28 g (51%) of [R]-(-)-N-Methyl-3-phenyl-3-(3-iodophenoxy)propylamine (Compound 3) as a pale yellow oil; R_f 0.29 (10% $MeOH/CH_2Cl_2$); $[\alpha]^{25}{}_D$- 0.71 (c 1.83, $CHCl_3$); ^1H NMR ($CDCl_3$, 250 MHz) δ 7.35 - 7.15 (m, 7H), 6.90 - 6.72 (m, 2H), 5.23 (dd, J = 4.6, 8.5 Hz, 1H) 3.50 (br s, 1H), 2.81 (br t, 1H), 2.48 (br s, 3H), 2.30 - 2.16 (m, 1H), 2.16 - 2.03 (m, 1H); FTIR (neat) 3400 (br, NH), 3100-300 (ArH), 29500-2750 (CH), 1575, 1475, 1225 cm^{-1}. MS m/l 367 (M + 1)

HCl gas was bubbled through a solution of Compound 3 in a minimum amount 1:1 ether: CH_2Cl_2. The cloudy solution was evaporated into dryness to give quantitatively the title compound (Compound 4) as a hygroscopic solid: mp 64°C $[\alpha]^{25}{}_D$ - 15.39 (c 1.37, $CHCl_3$); ^1H NMR $CDCl_3$, 250 MHz)δ 9.61 (br s, 2H), 7.35 - 7.18 (m, 7H), 6.90 - 6.72 (m, 2H), 5.32 (dd, J = 4.7, 8.5 Hz, 1H), 3.10 (m, 2H), 2.65 (br t, 3H), 2.41 (m, 2H).

Example 2

Preparation of [R]-(-)-N-Methyl-3-phenyl-3-(4-iodo-2-methylphenoxy)propylamine hydrochloride (Compound 7)

The compound [R]-(+)-1-chloro-3-phenyl-3-(4-iodo-2-methylphenoxy)propane (Compound 5) was prepared in the same manner as for the preparation of Compound 2 in Example 1, but using [S]-3-chloro-1-phenylpropanol (1.0 g, 5.88 mmol), 4-iodo-2-methylphenol (1.38 g, 5.88 mmol), triphenylphosphine (1.54 g, 5.88 mmol), and ethyl azodicarboxylate (0.93 mL, 1.04 g, 5.88 mmol) in THF (15 mL) at room temperature for 15 hours.

Workup and purification gave 1.60 g (70%) of Compound 5 as a thick pale yellow liquid: $[\alpha]^{25}_D$ + 14.02 (c 7.7, $CHCl_3$); ^1H NMR ($CDCl_3$, 250 MHz) δ 7.41 - 7.20 (m, 7H), 6.39 (d, J = 8.8 Hz, 1H), 5.34 (dd, J = 4.4, 8.8 Hz, 1H), 3.81 - 3.72 (m, 1H), 3.63 - 3.55 (m, 1H), 2.55 - 2.41 (m, 1H), 2.31 - 2.16 (m, 1H), 2.7 (s, 3H); FTIR (neat) 3080, 3020, 2970, 2915, 1585, 1485(s), 1450, 1390, 1360, 1290, 1245(s), 1180, 1130 cm^{-1}. Anal. $C_{17}H_{20}INO$: C,H.

The method for preparation of Compound 4 in Example 1 was modified. A mixture of Compound 5 (0.58 g, 1.5 mmol), aqueous methylamine (40%, 4 mL), and ethanol (1.5 mL) in a sealed tube was heated at 130°C for 3 hours. Workup and flash-column chromatography on silica gel (5% $MeOH/CH_2Cl_2$) afforded 0.25 g (44%) of [R]-(-)-N-methyl-3-phenyl-3-(4-iodo-2-methylphenoxy)propylamine (Compound 6) as a pale yellow oil: R_f 0.36 (12% $MeOH/CH_2Cl_2$); $[\alpha]^{25}_D$+ 11.98 (C 3.32, $CHCl_3$): ^1H NMR ($CDCl_3$, 250 MHz) δ 7.43 - 7.20 (m, 7H), 6.38 (d, J = 5.4 Hz, 1H); 5.23 (dd, J = 3.0, 5.4 Hz, 1H), 2.78 (br t, 2H), 2.45 (br s, 3H), 2.28 (2, 3H), 2.28 - 2.12 (m, 1H), 2.10 - 2.00 (m 1H).

HCl was bubbled through a solution of Compound 6 in a minimum amount of 1:1 ether/CH_2Cl_2. Removal of the solvent afforded a quantitative yield of the title compound (Compound 7) as a hygroscopic solid: mp 68°C $[\alpha]^{25}_D$- 8.34 (c 0.82, $CHCl_3$): ^1H NMR ($CDCl_3$, 250 MHz) δ 9.66 (br s, 2H), 7.41 - 7.19 (m, 7H), 6.38 (d, J = 8.8 Hz, 1H), 5.39 (dd, J = 4.4, 8.0 Hz, 1H), 3.12 (m, 2H), 2.61 (br t, 2H), 2.49 (m, 2H), 2.25 (s, 3H). Anal. $C_{17}H_{21}ClINO$: C, H, N.

Example 3

Preparation of [S]-(+)-N-Methyl-3-phenyl-3-(3-iodophenoxy)propylamine (Compound 11)

The compound [S]-(-)-1-chloro-3-phenyl-3-(3-iodophenoxy)propane (Compound 9) was prepared in the same manner as for preparation of Compound 2 in Example 1 but using [R]-3-chloro-1-phenylpropanol (1.0 g, 5.88 mmol). Workup and purification gave 1.70 g (78%) of Compound 9 as a thick colorless liquid: $[\alpha]^{25}_D$- 0.61 (c 6.55, $CHCl_3$); ^1H NMR;

($CDCl_3$), 250 MHz δ 7.37 - 7.14 (m, 7H), 6.90 - 6.75 (m, 2H), 5.33 (dd, J = 4.4, 8.7 Hz, 1H), 3.81 - 3.71 (m, 1H), 3.61 - 3.51 (m, 1H), 2.51 - 2.36 (m, 1H), 2.25 - 2.11 (m, 1H); IR (neat) 3090, 3070, 2980, 2900, 1580(s), 1470(s), 1410, 1360, 1280, 1220, 1160; spectra are the same as for Compound 2.

Compound 11 was prepared in the same manner as Compound 4. A mixture of Compound 9 (0.56 g, 1.50 mmol), aqueous methylamine (40%, 4mL), and ethanol (1.5 mL) in a sealed tube was heated at 130°C for three hours. After workup and flash-column chromatography (5% $MeOH/CH_2Cl_2$), the compound [S]-(+)-N-methyl-3-phenyl-3-(3-iodophenoxy)propylamine (Compound 10) (0.31 g, 57%) was obtained as a pale yellow oil: R_f 0.49 (10% $MeOH/CH_2Cl_2$); $[\alpha]^{25}_D$- 1.61 (c 1.06, $CHCl_3$); ^1H NMR ($CDCl_3$, 250 MHz) δ 7.37 - 7.19 (m, 7H), 6.90 - 6.75 (m, 2H), 5.22 (dd, J = 4.6, 8.5 Hz, 1H), 2.78 (br t, 2H), 2.45 (br s, 3H), 2.27 - 2.12 (m, 1H), 2.08 - 1.95 (m, 1H). FTIR (neat) 3400 (br, NH), 3100 - 300 (ArH), 2950 - 2750 (CH), 1590, 1460, 1226 cm^{-1}.

HCl gas was bubbled through a solution of Compound 10 in a minimum amount of 1:1 ether/CH_2Cl_2. Removal of the solvent afforded a quantitative yield of the title compound (Compound 11) as a hygroscopic solid: mp 62°C $[\alpha]^{25}_D$+ 16.42 (C 2.12, $CHCl_3$); ^1H NMR ($CDCl_3$, 250, MHz) δ 9.63 (br s, 2H), 7.35 - 7.18 (m, 7H), 6.89 - 6.72 (m, 2H), 5.32 (dd, J = 4.7, 8.5 Hz, 1H), 3.21 (m, 2H), 2.63 (br t, 3H), 2.42 (m, 2H): Anal. C_{16} H_{18} NIO: C, H, N.

Example 4

Preparation of {S}-(+)-N-Methyl-3-phenyl-3-(4-iodo-2-methylphenoxy)propylamine hydrochloride (Compound 14)

The compound [S]-(-)-1-chloro-3-phenyl-3-(4-iodo-2-methylphenoxy)propane (Compound 12) was prepared in the same manner as Compound 2 in Example 1 but using [R]-3-chloro-1-phenylpropanol (1.0 g, 5.88 mmol), 4-iodo-2-methylphenol (1.38 g, 5.88 mmol), triphenylphosphine (1.54 g, 5.88 mmol) and ethyl azodicarboxylate (0.93 mL, 1.04 g, 5.88 mmol) in THF (15 mL) at room temperature for 15 hours. Workup

and purification gave 1.58 g (69%) of Compound 12 as a thick pale yellow liquid: $[\alpha]^{25}{}_{D}$+ 14.97 (c 10.73, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.42 - 7.20 (m, 7H), 6.39 (d, J = 8.8 Hz, 1H), 5.34 (dd, J = 4.6, 8.8 Hz, 1H), 3.83 - 3.72 (m, 1H), 3.65 - 3.55 (m, 1H), 2.55 - 2.40 (m, 1H), 2.29 - 2.13 (m, 1H), 2.25 (s, 3H), FTIR (neat) 3050, 3015, 2950, 2900, 1600, 1480 (s), 1460, 1395, 1350, 1300, 1250(s), 1200, 1135 cm^{-1}. Anal. $C_{17}H_{20}INO$: C, H.

A mixture of Compound 12 (0.58 g, 1.50 mmol), aqueous methylamine (40%, 4 mL), and ethanol (1.50 mL) in a sealed tube was heated at 130°C for three hours. Workup and chromatography on silica gel (5% $MeOH/CH_2Cl_2$) afforded 0.27 g (48%) of [S]-(+)-N-methyl-3-phenyl-3-(4-iodo-2-methylphenoxy)propylamine (Compound 13) as a yellowish oil: R_f 0.25 (8% $MeOH/CH_2Cl_2$); $[\alpha]^{25}{}_{D}$- 11.5 (C 3.03, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.43 - 7.19 (m, 7H), 6.37 (d, J = 5.4 Hz, 1H), 5.23 (dd, J = 3.0, 5.4 Hz, 1H), 2.78 (br s, 2H), 2.45 (br s, 3H), 2.27 (s, 3H), 2.27 - 2.11 (m, 1H), 2.11 - 1.97 (m, 1H); FTIR (neat), 3400 (NH), 300 - 2550, 14990, 1250 cm^{-1}.

HCl gas was bubbled through a solution of Compound 13 in a minimum amount of 1:1 ether/CH_2Cl_2. The cloudy solution was evaporated into dryness to give quantitatively the title compound (Compound 14) as a hygroscopic solid: mp 66°C $[\alpha]^{25}{}_{D}$+ 6.43 (c 1.14, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 250 MHz) δ 9.68 (br s, 2H), 7.40 - 7.18 (m, 7H), 6.37 (d, J = 8.8 Hz, 1H), 5.38 (dd, J = 4.4, 8.0 Hz, 1H), 3.12 (br s, 2H), 2.60 (br t, 3H), 2.49 (m, 2H), 2.22 (s, 3H). MS. m/1 381 (M + 1).

Example 4

The affinity of the compounds prepared in Examples 1 - 4 to serotonin and norepinephrine uptake sites was studied using *in vitro* competetive binding assays. The results are presented in Table 3.

Table 3

Competition of serotonin and norepinephrine reuptake sites in rat brain tissue preparation

Compound	Serotonin Uptake [^{3}H]-Paroxetine K_i (nM)	Norepinephrine Uptake [^{3}H]-Nisoxetine IC_{50} (nM)
4	0.8	500
11	8.2	7000
7	5.0	20
14	0.8	9

There are several basic requirements for serotonin reuptake inhibitors as *in vivo* SPECT imaging agents. First, they should desirably be labeled with a suitable short-lived isotope emitting a medium energy gamma ray (100-300 KeV) and should be capable of being synthesized and purified rapidly. The compounds of this invention can be labeled with ^{123}I, an isotope emitting gamma energy of 159 KeV, as described previously. Second, they should be able to pass through the intact blood-brain barrier following intravenous injection. The compounds of this invention are neutral and lipid-soluble molecules. Preliminary studies of related compound radioiodinated fluoxetine showed good initial brain uptake and prolonged brain retention (0.68% and 0.63% dose/organ at two minutes and 8 hours, respectively). These results suggest that the compounds of this invention are feasible candidates as imaging agents for the central nervous system. Third, the compounds should exhibit high affinity and low nonspecific binding to the receptor. The test results provided in Example 4 suggest that the compounds of this invention meet this requirement.

Example 5

The biodistribution of [R]-(-)-N-methyl-3-phenyl-3-(4-^{123}I-2-methylphenoxy)propylamine hydrochloride (compound 7) in rats, after intravenous injection, was analyzed. Results are presented in Table 4 and indicate that moderate brain uptake (0.64-0.84% dose/organ) is found

consistently throughout the two hour period.

Table 4

Biodistribution in rats after an iv injection (% dose/organ) (n = 3)

Organ				
Blood	4.15±0.30	2.19±0.32	2.19±0.11	2.39±0.33
Heart	2.88±0.14	0.55±0.04	0.39±0.02	0.32±0.015
Muscle	9.05±1.20	22.77±4.86	21.49±2.44	19.63±1.89
Lung	18.26±1.70	9.36±1.52	9.11±0.48	6.81±0.76
Kidney	6.07±1.03	2.70±0.48	1.88±0.13	1.12±0.44
Spleen	0.48±0.38	1.09±0.32	1.05±0.08	0.79±0.05
Liver	15.61±3.34	23.56±3.61	22.12±1.74	24.52±1.82
Skin	7.37±0.49	6.75±1.35	9.39±1.30	6.92±0.83
Thyroid	0.094±0.023	0.07±0.02	0.06±0.02	0.04±0.008
Brain	0.64±0.08	0.80±0.04	0.84±0.051	0.68±0.01

Example 6

Preparation and Testing of Iodo-Fluoxetine (I-FXT)

The compound iodo-fluoxetine (Compound 15) was prepared via the synthesis illustrated in Figure 3. The hydrogen peroxide catalyzed iododestannylation gave [^{125}I]I-FXT in high yield (70%) and excellent purity (≥ 96%, HPLC). The biodistribution in rats (Table 5) showed good initial brain uptake and prolonged brain retention (0.68% and 0.63% dose/organ at 2 min. and 8 hr., respectively). High heart uptake was also observed with initial uptake of 2.3% at 2 min. and 0.3% at 8 hr. post injection. However, ex vivo autoradiography of rat brain sections at 2 hr. post i.v. injection showed a regional distribution pattern, which was not altered by pretreatment of paroxetine (10 mg/Kg, i.p.). In vitro binding studies indicated strong non-specific binding with prefrontal cortex membrane of rat brain. These data suggest that further animal studies of I-FXT are needed to identify the nature of in vivo brain uptake and retention.

Table 5

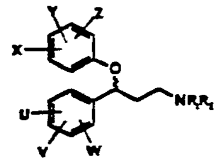
Biodistribution in rats after an iv injection (% dose/organ)

Organ	2 min.	15 min.	60 min.
Blood	3.03±0.40	1.71±0.31	3.16±0.36
Heart	2.27±0.31	1.14±0.04	0.43±0.05
Muscle	12.71±5.3	16.01±4.55	22.63±4.48
Lung	11.09±2.32	6.77±0.25	7.32±0.45
Kidney	4.16±0.36	4.05±0.44	2.32±0.38
Spleen	0.61±0.06	0.93±0.15	1.20±0.13
Liver	15.92±2.41	16.27±2.35	17.64±1.88
Skin	4.90±0.50	5.84±0.95	10.76±2.85
Thyroid	0.10±0.04	0.07±0.03	0.08±0.01
Brain	0.61±0.12	0.68±0.02	0.78±0.01

Organ	120 min.	240 min.	480 min.
Blood	3.62±0.24	4.99±0.70	7.61±1.11
Heart	0.48±0.02	0.28±0.01	0.32±0.03
Muscle	24.22±0.68	20.38±2.67	19.90±2.61
Lung	7.21±0.36	7.57±2.36	5.00±0.46
Kidney	1.82±0.21	1.18±0.17	1.11±0.06
Spleen	1.09±0.07	0.71±0.11	0.52±0.048
Liver	11.55±0.78	11.52±0.91	16.47±2.03
Skin	10.08±0.78	8.27±0.75	10.78±0.07
Thyroid	0.10±0.02	0.14±0.001	0.22±0.06
Brain	0.84±0.073	0.70±0.031	0.61±0.07

What is claimed is:

1. Compounds of the formula



where each of U, V, W, X, Y and Z is independently selected from the group consisting of hydrogen; halogen; $C_1 - C_4$ alkyl; $C_1 - C_4$ alkyl substituted with one or more moieties selected from halogen atoms and hydroxy groups; $C_1 - C_4$ alkoxy; $C_1 - C_4$ alkoxy substituted with one or more moieties selected from halogen atoms and hydroxy groups; $C_1 - C_6$ heterocycles; $C_1 - C_4$ thioalkyl; NR_3R_4; $-R_5 -A - R_6$; and $-A-R_7$; CN; SO_2R_8; $-NHCONH_2$; and $C(O)NR_3R_4$;

each of R_1, R_2, R_3 and R_4 is independently selected from the group consisting of hydrogen and $C_1 - C_4$ alkyl;

each of R_5 and R_6 is independently a $C_1 - C_6$ alkyl;

R_7 is selected from the group consisting of H, $C_1 - C_6$ alkyl, $C_1 - C_6$ heterocycles or $-A-R_5$;

R_8 is selected from the group consisting of $C_1 - C_4$ alkyl and NR_3R_4;

A is selected from the group consisting of S, N and O;

provided that at least one of U, V, W, X, Y and Z is a halogen atom;

and pharmaceutically acceptable salts thereof.

2. Compounds of Claim 1 where one of X, Y and Z is alkyl.

3. Compounds of Claim 1 where one of X, Y and Z is halogen.

4. Compounds of Claim 3 where one of X, Y and Z is ^{123}I.

5. Compounds of Claim 2 where X is a 2-alkyl substituent.

6. Compounds of Claim 2 where Y is a 4-halogen

substituent.

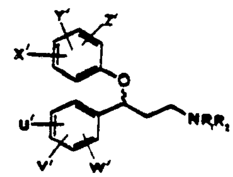
7. Compounds of Claim 1 where R_1 is H and R_2 is CH_3.

8. Compounds of Claim 5 where Y is a 4-halogen substituent.

9. Compounds of Claim 8 where R_1 is H and R_2 is CH_3.

10. The compound N-methyl-3-phenyl-3-(4-iodo-2-methylphenoxy)propylamine.

11. Compounds of the formula



II

where one of U', V', W', X', Y' and Z' is selected from the group consisting of $Sn(R)_3$, $Si(R)_3$ and HgR, where R is C_1 - C_5 alkyl; and the others are selected from the group consisting of hydrogen; halogen; C_1 - C_4 alkyl; C_1 - C_4 alkyl substituted with one or more moieties selected from halogen atoms and hydroxy groups; C_1 - C_4 alkoxy; C_1 - C_4 alkoxy substituted with one or more moieties selected from halogen atoms and hydroxy groups; C_1 - C_6 heterocycles; C_1 - C_4 thioalkyl; NR_3R_4; $-R_5$ -A - R_6; and $-A-R_7$; CN; SO_2R_8; $-NHCONH_2$; and $C(O)NR_3R_4$;

each of R_1, R_2, R_3 and R_4 is independently selected from the group consisting of hydrogen and C_1 - C_4 alkyl;

each of R_5 and R_6 is independently a C_1 - C_6 alkyl;

R_7 is selected from the group consisting of H, C_1 - C_6 alkyl, C_1 - C_6 heterocycles or $-A-R_5$;

R_8 is selected from the group consisting of C_1 - C_4 alkyl and NR_3R_4; and

A is selected from the group consisting of S, N and O.

12. A serotonin receptor imaging agent comprising a compound of Claim 1 wherein one of U, V, W, X, Y and Z is a radioactive halogen isotope.

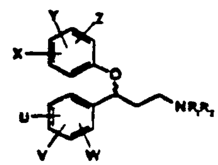
13.. A method of imaging serotonin receptors in a patient comprising administering to said patient an effective

quantity of an imaging agent of Claim 12 and measuring the gamma ray or photo emissions therefrom.

SEROTONIN REUPTAKE INHIBITORS FOR S.P.E.C.T IMAGING

Abtract of the Invention

Disclosed are novel compounds for CNS neurotransmitter systems, especially for the neurotransmitter serotonin, which have the formula



where each of U, V, W, X, Y and Z is independently selected from the group consisting of hydrogen; halogen; C_1 - C_4 alkyl; C_1 - C_4 alkyl substituted with one or more moieties selected from halogen atoms and hydroxy groups; C_1 - C_4 alkoxy; C_1 - C_4 alkoxy substituted with one or more moieties selected from halogen atoms and hydroxy groups; C_1 - C_6 heterocycles; C_1 - C_4 thioalkyl; NR_3R_4; $-R_5$ -A - R_6; and -A-R_7; CN; SO_2R_8; -$NHCONH_2$; and C(O)NR_3R_4;

each of R_1, R_2, R_3 and R_4 is independently selected from the group consisting of hydrogen and C_1 - C_4 alkyl;

each of R_5 and R_6 is independently a C_1 - C_6 alkyl;

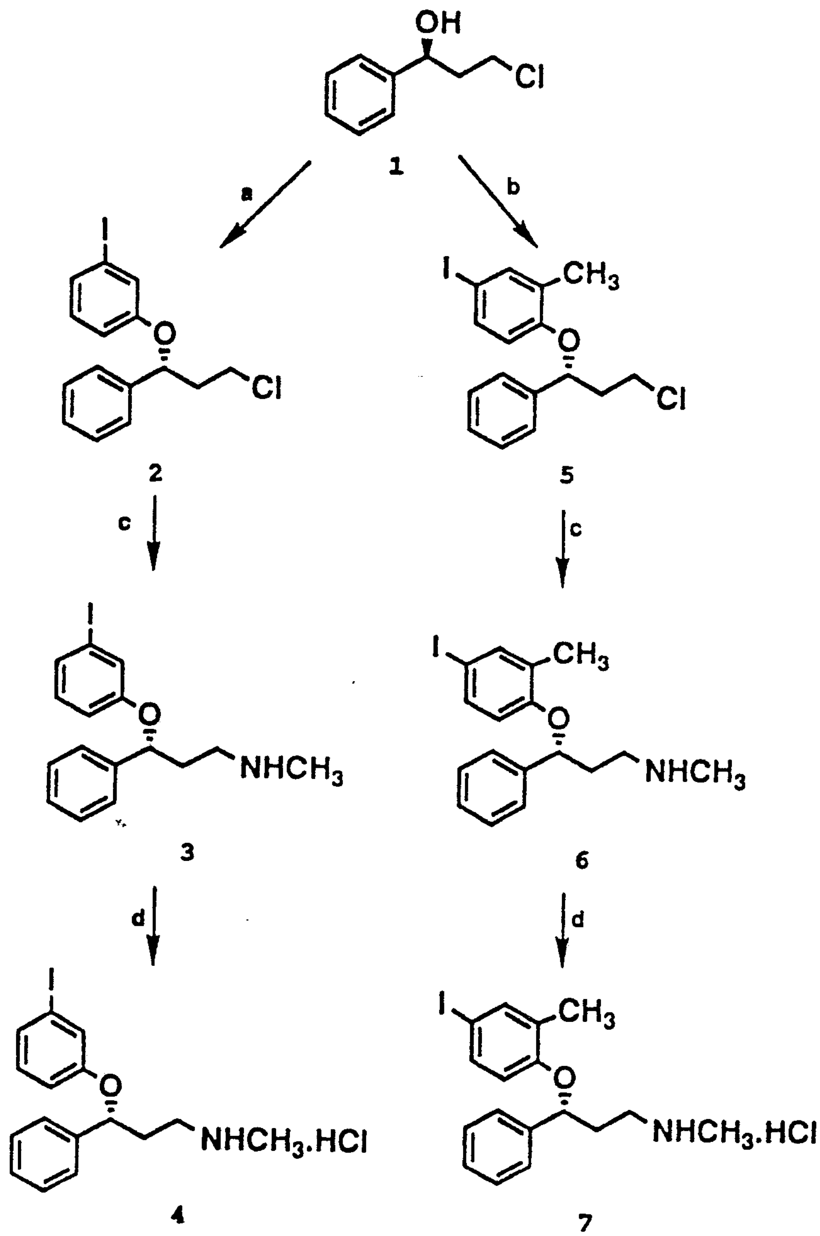
R_7 is selected from the group consisting of H, C_1 - C_6 alkyl, C_1 - C_6 heterocycles or -A-R_5;

R_8 is selected from the group consisting of C_1 - C_4 alkyl and NR_3R_4;

A is selected from the group consisting of S, N and O;

provided that at least one of U, V, W, X, Y and Z is a halogen atom;

and pharmaceutically acceptable salts thereof.



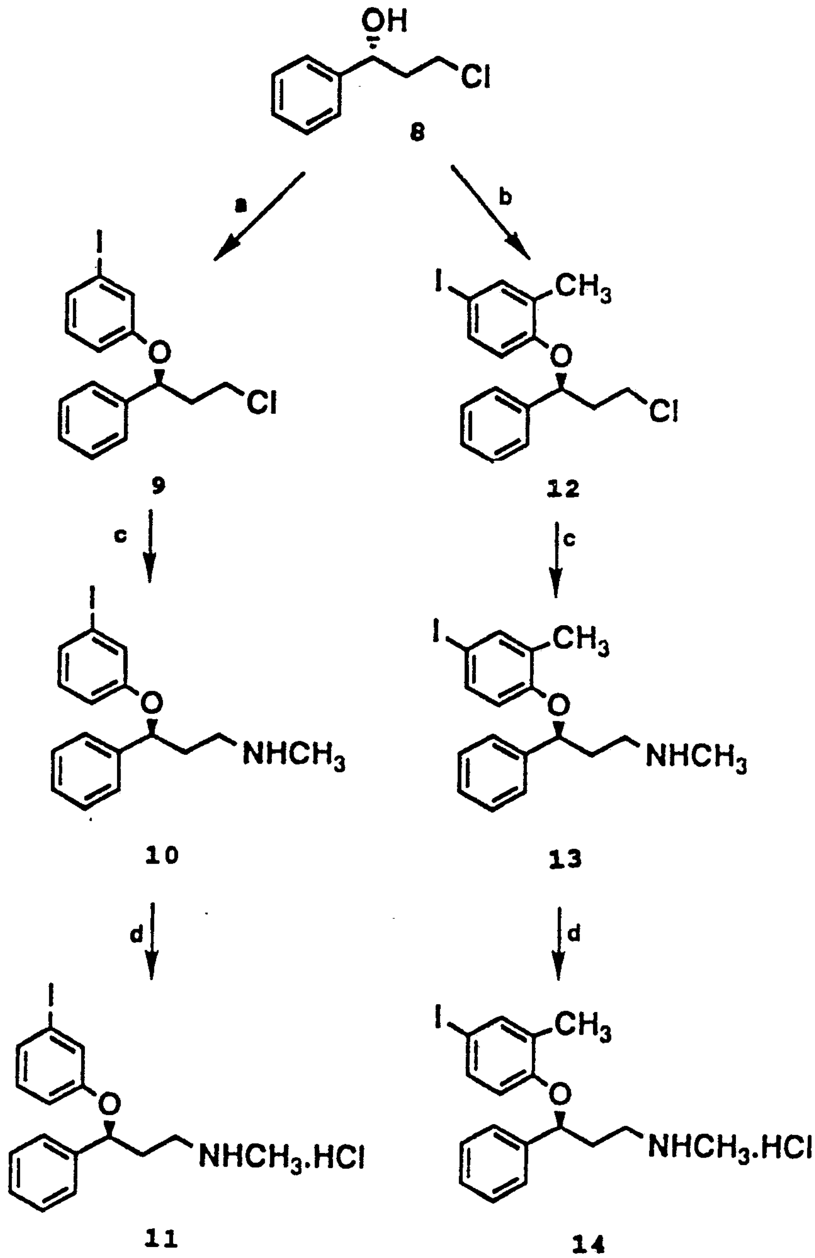
a) 3-iodophenol, DEAD, PPh_3, THF, rt, 15h

b) 2-methyl-4-iodophenol, DEAD, PPh_3, THF, rt, 15h

c) 40%$NHCH_3$, ethanol, 130 °C, 3h

d) HCl gas

FIGURE 1



a) 3-iodophenol, DEAD, PPh_3, THF, rt, 15h

b) 2-methyl-4-iodophenol, DEAD, PPh_3, THF, rt, 15h

c) 40%$NHCH_3$, ethanol, 130 °C, 3h

d) HCl gas

FIGURE 2

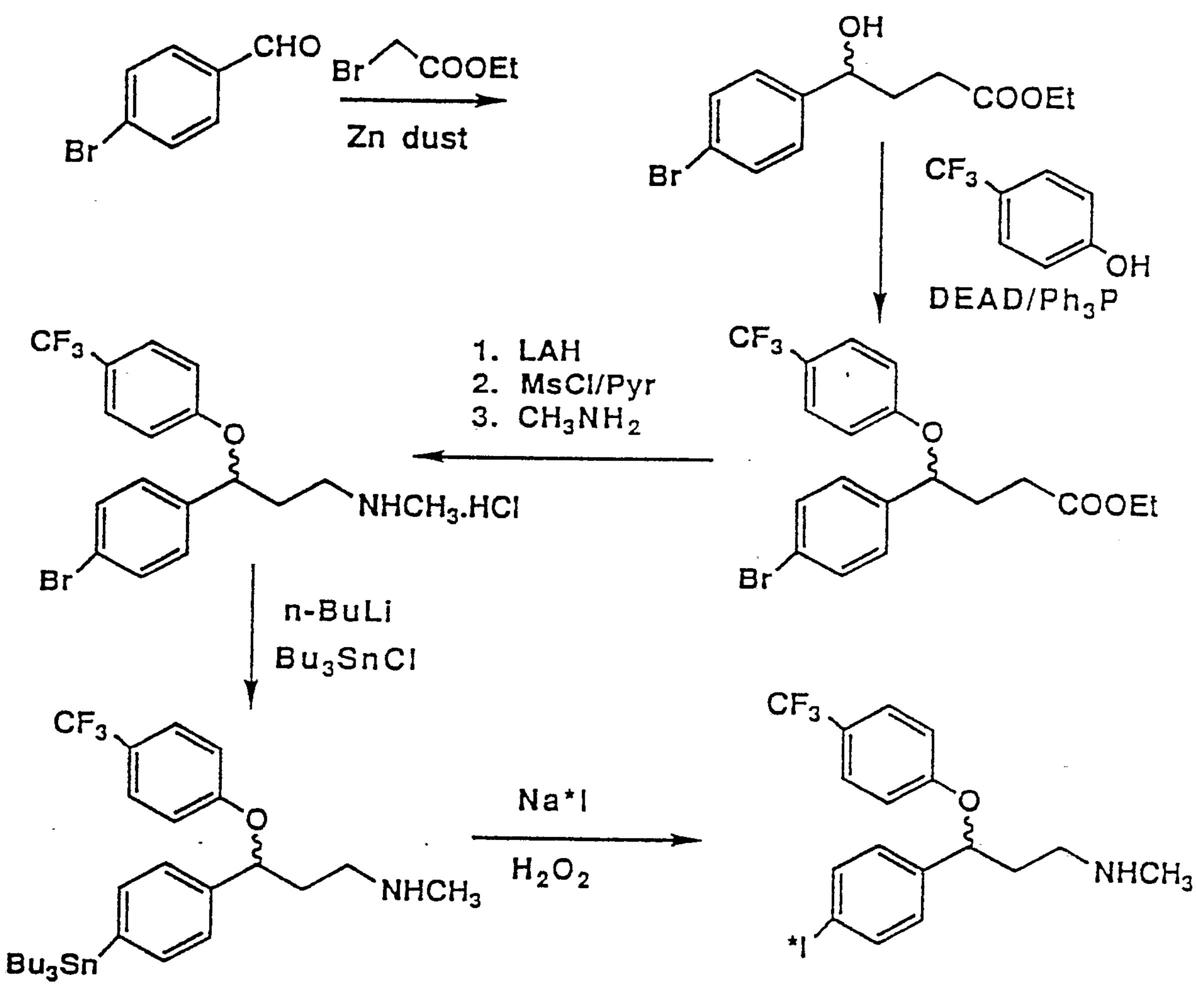

CHO
Br
Br COOEt
Zn dust
OH
COOEt
Br
CF3
OH
DEAD/Ph3P
1. LAH
2. MsCl/Pyr
3. CH3NH2
CF3
O
NHCH3.HCl
Br
CF3
O
COOEt
Br
n-BuLi
Bu3SnCl
CF3
O
NHCH3
Bu3Sn
Na*I
H2O2
CF3
O
NHCH3
*I

FIGURE 3